Patient Related Outcome Measures

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ORIGINAL RESEARCH

Correlations between patient-reported outcomes and self-reported characteristics in adults with hemophilia B and caregivers of children with hemophilia B: analysis of the B-HERO-S study

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Patient Related Outcome Measures

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Purpose: Pain, anxiety, depression, and other aspects of health-related quality of life (HRQoL) are important issues for people with hemophilia and caregivers of children with hemophilia. Patient-reported outcome (PRO) instruments may be used to assess aspects of HRQoL; however, the use of PROs in clinical management of patients with hemophilia is limited and inconsistent. The Bridging Hemophilia B Experiences, Results and Opportunities Into Solutions (B-HERO-S) study evaluated the impact of hemophilia B on HRQoL and other psychosocial aspects in affected adults and caregivers of children with hemophilia B. This post hoc analysis assessed correlations between PRO scores and psychosocial questions commonly asked in comprehensive care settings among B-HERO-S respondents.

Patients and methods: B-HERO-S consisted of two online surveys, one administered to adults with hemophilia B (n=299) and one administered to caregivers of children with hemophilia B (n=150). The adult survey included EQ-5D-5L with visual analog scale, BPI, HAL, and PHQ-9. The caregiver survey included PHQ-9 and GAD-7. Questions related to demographics, hemophilia treatment, and psychosocial questions asked in comprehensive care visits were also included in the surveys. A post hoc analysis was performed to assess correlations between responses to selected psychosocial questions with PRO scores.

Results: For adults with hemophilia B, greater pain severity and pain interference scores were associated with work-related problems, functional limitations, and relationship, psychological, and treatment issues. Significant correlations were also noted between some of these psychosocial outcomes and depressive symptoms. For caregivers, greater depression and anxiety were associated with employment issues, their child's functional, relationship, and psychological issues, having had difficulty or concerns with treatment/factor availability or affordability, and having less frequent HTC visits.

Conclusion: High correlations were observed between PRO scores measuring pain, depression, and anxiety and questions commonly used in the comprehensive care setting to assess the psychosocial impact of hemophilia.

Keywords: health-related quality of life, depression, anxiety, employment, relationships

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Introduction

Hemophilia B is a congenital bleeding disorder caused by a deficiency of factor IX.[1] Repeated joint bleeds cause hemophilic arthropathy,[2] often leading to pain and functional impairment.[3,4] Having hemophilic arthropathy negatively affects various aspects of health-related quality of life (HRQoL), including pain, anxiety, and depression.[3,5–7]

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These outcomes are important to both patients and caregivers of children with hemophilia. The Hemophilia Experiences, Results and Opportunities (HERO) study previously surveyed individuals with hemophilia A and hemophilia B to assess various outcomes related to HRQoL.[8] The patient population across 10 countries was predominantly individuals with hemophilia A (74%), providing information about HRQoL in relatively few patients with hemophilia B.

Additionally, although hemophilia is an X-linked disorder primarily affecting males, females can have hemophilia due to lyonization of one X-chromosome (<40% factor activity) or can be carriers with normal factor levels who can also exhibit bleeding symptoms.[9] The Bridging Hemophilia B Experiences, Results, and Opportunities Into Solutions (B-HERO-S) study was developed to evaluate the impact of hemophilia on psychosocial issues and other components of HRQoL for men and women with mild, moderate, or severe hemophilia B and caregivers of children with hemophilia B.

Patient-reported outcome (PRO) instruments may be used to assess aspects of HRQoL. The Pain, Functional Impairment, and Quality of Life (P-FiQ) study investigated the reliability and validity of several PRO instruments, including the five-level version of the EuroQol five-dimensional health status measure (EQ-5D-5L), 36-Item Short Form Survey (SF-36), Brief Pain Inventory v2 Short Form (BPI), and Hemophilia Activities List (HAL), in adults with hemophilia A and B in the treatment center setting.[10] Additional analyses using the P-FiQ data demonstrated associations among many of these outcomes that were independent of an individual's joint disease status (measured by the physical therapist-administered Hemophilia Joint Health Score [HJHS]), suggesting that factors beyond joint disease contribute to hemophilia's overall impact on patient health and well-being.[6] B-HERO-S also assessed the reliability and validity of an overlapping set of mostly generic instruments (EQ-5D-5L, BPI, Patient Health Questionnaire [PHQ-9], and Generalized Anxiety Disorder 7-item [GAD-7] scale) and one disease-specific PRO instrument (HAL) in men and women, including those with mild or moderate hemophilia B, as well as two PRO instruments (PHQ-9, GAD-7) in caregivers of affected children.

Psychosocial issues and/or functional impairment have been assessed in adults with hemophilia and caregivers of children with hemophilia by the Centers for Disease Control and Prevention (CDC) Universal Data Collection (UDC)[11] program and the HERO,[3] B-HERO-S,[12] and P-FiQ[7] studies. This paper describes a post hoc analysis of data from the B-HERO-S study that aimed to assess correlations between PRO domain scores and some of these psychosocial questions commonly asked in comprehensive care settings.

Materials and methods

Study design

Methods for the B-HERO-S study have been previously described.[12] In brief, the study recruited participants through the social media outlets and email lists for patient advocacy groups in the United States (Coalition for Hemophilia B, Hemophilia Federation of America, and National Hemophilia Foundation). The study included adults (over 18 years of age) with hemophilia B (n=299) or caregivers of a child (less than 18 years of age) with hemophilia B (n=150) and was open to people with hemophilia B of any severity, with or without inhibitors, including women with hemophilia B and caregivers of girls with hemophilia B. The study survey of approximately 100 questions was administered online between September 24 and November 2, 2015, and was approved by the Central Institutional Review Board (Quorum Review IRB, Seattle, WA, USA). The IRB waived informed consent for the study due to minimal risk criteria. Those who volunteered to participate in the survey were provided with written information about the nature, extent, design, and conduct of the survey through an IRB-approved informational letter posted on the websites of the three patient advocacy organizations through which participants were recruited. In addition, there were elements of informed consent language incorporated into a statement which participants affirmed agreement with electronically prior to entering the formal survey. Minimal consent language included informing subjects of the right to withdraw from the survey by discontinuing at any time while completing the survey, confidentiality and anonymity of results, and no personal health information being provided to the sponsor. After reading the survey information, participants affirmed their willingness to participate in the survey by ticking the "Agree to proceed" checkbox on the computer screen.

In order to better understand the psychosocial impact of hemophilia on both adults living with hemophilia B and the families of children with hemophilia, two surveys, one for adults with hemophilia B and one for caregivers of children with hemophilia B, were administered. Participants provided demographic and clinical information, including hemophilia B severity, treatment methods, self-reported

illnesses, and employment status. The psychosocial question battery was based largely on those developed for the HERO study by an international expert panel, informed initially by a literature review[13] and qualitative interactive survey[14,15] that resulted in the 10 country qualitative survey instruments.[8] Additional clarifying questions were added based upon issues raised by expert panel and authors (eg, impact of prior relationships and disclosure)[16] and feedback from global and regional HERO summit.[17] Additionally, five PRO instruments were administered: EQ-5D-5L with visual analog scale (VAS), BPI, HAL, PHQ-9 (completed by both adults with hemophilia B and caregivers of children with hemophilia B), and GAD-7 (completed by caregivers only). Specific PROs were chosen with preference for generic instruments that can be compared against other disease states (EQ-5D-5L, BPI) or map to diagnostic classifications (PHQ-9, GAD-7). Survey questions and response options are listed in Tables S1 and S2.

PRO instruments

EQ-5D-5L measures current overall health status. A descriptive section assesses five dimensions (mobility [MO], self-care [SC], usual activities [UA], pain/discomfort [PD], and anxiety/depression [AD])[18,19] and index scores are calculated with a population-specific tariff using the EuroQoL index value calculator.[20] The VAS segment uses an electronic version of the printed scale on which participants indicate their current health state using a 100-point scale "worst health you can imagine" at 0 and "best health you can imagine" at 100.

BPI evaluates pain severity and interference in the last week using scores that range from 0 ("no pain" or "does not interfere") to 10 ("pain as bad as you can imagine" or "complete interference"). The averages of four severity domains (worst pain [WP], least pain [LP], average pain [AP], and current pain [CP]) were used to calculate BPI pain severity composite score (PS) and the averages of seven interference domains (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) were used to calculate the BPI pain interference composite score (PI).

HAL scores the level of difficulty to perform an activity within the past month for 42 items across 7 domains (lying/sitting/kneeling/standing, function of the legs, function of the arms, use of transportation, self-care, household tasks, and leisure activities/sports). HAL scores range from 0 to 100, where higher scores indicate better functional status. HAL includes an overall score (calculated from the individual domain scores) as well as three component scores (upper extremity [UE] activities, basic lower extremity [BLE] activities, and complex lower extremity [CLE] activities).

PHQ-9 evaluates depression using nine items from the "Diagnostic and Statistical Manual of Mental Disorders: DSM-IV" components of depression, scoring each item on a scale of 0 (not at all) to 3 (every day). Total PHQ-9 score is calculated as the sum of the item scores and ranges from 0 to 27. This total score correlates to the following diagnostic categories of depression: 0–4, no depression; 5–9, mild depression; 10–14, moderate depression; 15–19, moderately severe depression; 20–27, severe depression.[21]

GAD-7 assesses anxiety using a 7-item scale based on the "DSM-IV" elements of generalized anxiety disorder. The 7 items are each scored from 0 (not at all) to 3 (nearly every day). The sum of the item scores is used to calculate the total GAD-7 score, which ranges from 0 to 21 and correlates to the following diagnostic categories of anxiety: 5–9, mild anxiety; 10–14, moderate anxiety; ≥15, severe anxiety.[22]

Statistical analysis

PRO scores were calculated according to standard protocols.[18,21–25] A post hoc analysis was performed to assess bivariate correlations between responses to selected psychosocial survey questions and EQ-5D-5L (MO/SC/UA/PD/AD, Index, VAS), BPI (WP/LP/CP/AP, PS, PI), HAL (UE, BLE, CLE, Overall), PHQ-9, and GAD-7 (caregiver only) via Pearson correlations. Correlations of $r \geq 0.37$ were considered high, $0.24 \leq r < 0.37$ were considered moderate, and $r < 0.24$ were considered weak.[26]

Results

Adults with hemophilia B

B-HERO-S included 299 adults with hemophilia (213 men, 86 women). Demographics and treatment characteristics have been previously reported.[12] The majority of participants had moderate (63%) or mild (25%) hemophilia B. PRO results including EQ-5D-5L, BPI, HAL, and PHQ-9 have been previously reported.[27]

Correlations between PROs and psychosocial and functional questions

Work

Scores on PROs indicating worse overall health (lower EQ-5D-5L Index/VAS), increasing pain (BPI PS/PI), and decreased function (HAL) were all associated with

negative impacts of hemophilia B on work. These impacts included not working due to complications from hemophilia, increasing negative experiences with work/career, and negative experiences with telling an employer or a manager. In contrast, increasing satisfaction with support from an employer or a manager was associated with improved HRQoL (Table 1).

Function and recreational activities

Increasing limitations on functional abilities, reduced engagement in activities, sometimes/always using cane/crutches/walker in the past 6 months, and sometimes/always using wheelchair in the past 6 months had strong, negative correlations with overall health (EQ-5D-5L Index/VAS) and physical function (HAL Overall) and strong, positive correlations with increased pain (BPI PS/PI). Use of a cane/crutches/walker or wheelchair was positively correlated with worsening depression (PHQ-9; Table 2). Increasing negative impact of hemophilia on ability to engage in activities was positively correlated with pain (BPI PS/PI) and negatively correlated with overall health (EQ-5D-5L Index/VAS) and reduced function (HAL Overall).

Family and relationships

Hemophilia affecting relationships with partners or prospective partners was negatively correlated with overall health measures (EQ-5D-5L VAS) and positively correlated with one measure of pain (BPI LP). In contrast, increasing satisfaction with support from current partner regarding hemophilia was positively correlated with overall health (EQ-5D-5L Index/VAS) and physical function (HAL BLE) and negatively correlated with increased pain (BPI WP/LP/AP/CP/PS/PI). Increasing impact of hemophilia on the quality of sex life was associated with decreased overall health measures (EQ-5D-5L Index/VAS) and increased pain (BPI LP/AP/CP/PS; Table 3).

Negative experiences telling friends about hemophilia and being bullied by peers because of hemophilia were both correlated with reduced overall health and physical function (EQ-5D-5L MO/SC/UA/AD/Index/VAS and HAL UE/BLE/Overall) and increased pain scores (BPI LP/AP/CP/PS/PI). In contrast, increased satisfaction with support from friends was positively correlated with overall health (EQ-5D-5L Index/VAS) and physical function (HAL Overall) and negatively correlated with pain as measured by BPI (LP/AP/CP/PS/PI; Table 3).

Both negative experiences with telling colleagues at work/school about hemophilia and being bullied by colleagues at work/school because of hemophilia had strong, negative correlations with overall health (EQ-5D-5L Index/VAS) and physical function (HAL Overall; Table 3).

Psychological/stress

Experiencing a stressful event (specifically loss of job item response) and having received psychological treatment in the past 5 years were strongly correlated with increased pain (BPI WP/LP/AP/CP/PS/PI), increased severity of depressive symptoms (PHQ-9), and increased severity of pain, anxiety, and depression as measured by EQ-5D-5L items (MO/SC/UA/PD/AD/Index/VAS). However, these factors were weakly correlated with physical function scores (HAL; Table 4).

Strong, positive correlations were seen between having specific psychological treatment related to hemophilia and increased pain scores, but there was not a strong correlation between this factor and severity of depressive symptoms as measured by the PHQ-9 (Table 4).

Access to and responsibility for factor/treatment

Self-responsibility for hemophilia care (vs somebody else primarily responsible) showed strong negative correlations with increased pain (BPI PS/PI) and positive correlations with increased HRQoL on EQ-5D-5L Index/VAS and HAL Overall scores (Table 5).

Taking routine factor treatment at any infusion interval (vs on-demand treatment for bleeding) showed positive correlations with pain (BPI WP/LP/AP/CP/PS/PI) and negative correlations with overall health (EQ-5D-5L Index/VAS) and functional measures (HAL Overall; Table 5).

Overall, concerns about or difficulties with obtaining factor products due to availability in the last 5 years were more strongly correlated with reduced HRQoL than was concern about access in the next 5 years. Strong, positive correlations were seen between difficulty obtaining factor over the last 5 years and measures of worsening HRQoL on most PRO instruments. In addition, strong, negative correlations were seen between difficulty obtaining factor over the last 5 years and improving overall health (EQ-5D-5L Index/VAS) but not functional measures (HAL scores). Anticipated difficulty in the next 5 years was most strongly correlated with pain (BPI PS/PI) and negatively correlated with overall health and physical function (EQ-

Table 1 Pearson correlation assessment between hemophilia impact on work and PRO scores in adults with hemophilia B

Survey Question	EQ-5D-5L Mobility	EQ-5D-5L Self-care	EQ-5D-5L Usual Activities	EQ-5D-5L Pain/ Discomfort	EQ-5D-5L Anxiety/ Depression	EQ-5D-5L Index Score[a]	EQ-5D-5L Overall Health VAS Score	BPI Worst Pain[b]	BPI Least Pain[b]
Not working (vs working full or part-time)	−0.291	−0.055[g]	−0.119[g]	−0.315	−0.127[g]	0.155[g]	−0.244[g]	−0.285	0.106[g]
Not working due to complications from hemophilia	**0.506**	0.201[g]	0.183[g]	**0.472**	**0.545**	**−0.533**	**−0.487**	**0.472**	0.305[g]
Current treatment allows me to work	−0.266	−0.257	**−0.426**	**−0.402**	−0.323	0.343	0.208	−0.353	−0.36
Increasing negative experiences with work/ career	**0.523**	**0.445**	**0.492**	**0.449**	**0.399**	**−0.591**	**−0.587**	0.367	**0.439**
Increasing satisfaction with support from employer or manager	−0.319	−0.292	−0.321	−0.19	−0.282	**0.375**	0.314	−0.219	−0.315
Negative experience with telling employer or manager	**0.511**	**0.51**	**0.511**	0.357	0.352	**−0.57**	**−0.678**	**0.424**	**0.573**

Survey Question	BPI Average Pain[b]	BPI Current Pain[b]	BPI Pain Severity[c]	BPI Pain Interference[d]	HAL Upper Extremity[e]	HAL Basic Lower Extremity[e]	HAL Complex Lower Extremity[e]	HAL Overall Score[e]	PHQ-9 Total Score[f]
Not working (vs working full or part-time)	0.019[g]	−0.077[g]	−0.075[g]	−0.247[g]	0.112[g]	0.160[g]	0.254[g]	0.145[g]	**−0.531**
Not working due to complications from hemophilia	0.365[g]	**0.428**[g]	**0.459**	**0.394**[g]	**−0.522**	**−0.529**	**−0.538**	**−0.563**	0.346[g]
Current treatment allows me to work	**−0.403**	−0.349	**−0.398**	**−0.428**	0.238	0.238	0.256	0.278	**−0.506**
Increasing negative experiences with work/career	**0.443**	**0.467**	**0.471**	**0.52**	**−0.594**	**−0.564**	**−0.499**	**−0.617**	0.125[g]
Increasing satisfaction with support from employer or manager	−0.338	**−0.378**	−0.35	−0.328	0.357	0.234	0.245	0.322	0.002[g]
Negative experience with telling employer or manager	**0.54**	**0.62**	**0.601**	**0.572**	**−0.693**	**−0.561**	**−0.45**	**−0.654**	0.034[g]

Notes: [a]Range, −0.011–1.0 (higher scores indicate better quality of life or functional status). [b]Range, 0–10 (higher scores indicate greater pain severity or pain interference). [c]Pain severity score is the average of 4 severity scores (worst, least, average, current). [d]Pain interference score is the average of 7 interference scores. [e]Range, 0–100 (higher scores indicate better quality of life or functional status). [f]Range, 0–27 (higher scores indicate more severe depression). [g]Not significant. Negative attributes are shown in red. Inverse correlations are highlighted in gray. Correlations highlighted in bold are considered high ($r \geq 0.37$).

Abbreviations: BPI, Brief Pain Inventory v2 Short Form; HAL, Hemophilia Activities List; PHQ-9, Patient Health Questionnaire; VAS, visual analog scale.

Table 2 Pearson correlation assessment between hemophilia impact on functional and recreational activities and PRO scores in adults with hemophilia B

Survey Question	EQ-5D-5L Mobility	EQ-5D-5L Self-care	EQ-5D-5L Usual Activities	EQ-5D-5L Pain/ Discomfort	EQ-5D-5L Anxiety/ Depression	EQ-5D-5L Index Score[a]	EQ-5D-5L Overall Health VAS Score	BPI Worst Pain[b]	BPI Least Pain[b]
Increasing limitation in functional abilities and engagement in activities	**0.496**	**0.44**	**0.508**	0.348	**0.45**	**−0.521**	**−0.502**	**0.395**	**0.415**
Sometimes/always used cane/ crutches/walker in the past 6 months	**0.474**	**0.509**	**0.628**	**0.6**	**0.535**	**−0.59**	**−0.424**	**0.547**	**0.631**
Sometimes/always used wheelchair in the past 6 months	**0.511**	**0.524**	**0.538**	**0.566**	**0.519**	**−0.581**	**−0.484**	**0.498**	**0.579**
Increasing negative impact of hemophilia on ability to engage in activities	**0.469**	**0.341**	**0.405**	**0.416**	0.358	**−0.45**	**−0.502**	**0.425**	0.287
Increasing treatment adjustment to accommodate participation in activities	**0.391**	**0.453**	**0.426**	**0.378**	**0.507**	**−0.537**	**−0.457**	**0.418**	**0.439**

Survey Question	BPI Average Pain[b]	BPI Current Pain[b]	BPI Pain Severity[c]	BPI Pain Interference[d]	HAL Upper Extremity[e]	HAL Basic Lower Extremity[e]	HAL Complex Lower Extremity[e]	HAL Overall Score[e]	PHQ-9 Total Score[f]
Increasing limitation in functional abilities and engagement in activities	**0.441**	**0.438**	**0.46**	**0.467**	**−0.47**	**−0.468**	**−0.417**	**−0.508**	0.248
Sometimes/always used cane/crutches/walker in the past 6 months	**0.594**	**0.582**	**0.644**	**0.618**	**−0.483**	**−0.446**	**−0.403**	**−0.52**	**0.551**
Sometimes/always used wheelchair in the past 6 months	**0.566**	**0.582**	**0.609**	**0.59**	**−0.409**	**−0.408**	−0.344	**−0.468**	**0.432**
Increasing negative impact of hemophilia on ability to engage in activities	0.34	0.342	**0.373**	**0.446**	**−0.516**	**−0.488**	**−0.53**	**−0.548**	0.16
Increasing treatment adjustment to accommodate participation in activities	**0.492**	**0.472**	**0.496**	**0.477**	**−0.434**	**−0.421**	−0.304	**−0.442**	0.204

Notes: [a]Range, −0.011–1.0 (higher scores indicate better quality of life or functional status). [b]Range, 0–10 (higher scores indicate greater pain severity or pain interference). [c]Pain severity score is the average of 4 severity scores (worst, least, average, current). [d]Pain interference score is the average of 7 interference scores. [e]Range, 0–100 (higher scores indicate better quality of life or functional status). [f]Range, 0–27 (higher scores indicate more severe depression). Negative attributes are shown in red. Inverse correlations are highlighted in gray. Correlations highlighted in bold are considered high ($r \geq 0.37$).

Abbreviations: BPI, Brief Pain Inventory v2 Short Form; HAL, Hemophilia Activities List; PHQ-9, Patient Health Questionnaire; VAS, visual analog scale.

Table 3 Pearson correlation assessment between hemophilia impact on family and relationships and PRO scores in adults with hemophilia B

Survey Question	EQ-5D-5L Mobility	EQ-5D-5L Self-care	EQ-5D-5L Usual Activities	EQ-5D-5L Pain/ Discomfort	EQ-5D-5L Anxiety/ Depression	EQ-5D-5L Index Score[a]	EQ-5D-5L Overall Health VAS Score	BPI Worst Pain[b]	BPI Least Pain[b]
Hemophilia affected relationship with (prospective) partners	0.153	0.302	0.29	0.119	0.245	−0.294	**−0.451**	0.146	**0.38**
Increasing satisfaction with support from partner regarding hemophilia	−0.358	**−0.464**	**−0.502**	−0.343	**−0.486**	**0.499**	**0.532**	**−0.397**	**−0.575**
Hemophilia affected the quality of sex life	0.209[g]	0.131[g]	0.26	0.362	**0.427**	**−0.389**	**−0.477**	0.246[g]	**0.431**
Increasing satisfaction with support from friends	−0.331	−0.296	−0.323	−0.187	−0.366	**0.409**	**0.488**	−0.258	**−0.466**
Negative experiences with telling friends about hemophilia	**0.414**	**0.402**	**0.379**	0.293	**0.388**	**−0.478**	**−0.492**	0.282	**0.436**
Bullied by peers because of hemophilia	**0.438**	**0.463**	0.366	0.281	**0.426**	**−0.529**	**−0.543**	0.343	**0.463**
Negative experiences with telling colleagues at work/school about hemophilia	0.303	**0.377**	0.358	0.191	0.346	**−0.424**	**−0.498**	0.248	0.358
Bullied by colleagues at work/school because of hemophilia	0.272	0.368	0.272	0.125	0.278	**−0.393**	**−0.49**	0.254	0.299

(*Continued*)

(Continued)

Survey Question	BPI Average Pain[b]	BPI Current Pain[b]	BPI Pain Severity[c]	BPI Pain Interference[d]	HAL Upper Extremity[e]	HAL Basic Lower Extremity[e]	HAL Complex Lower Extremity[e]	HAL Overall Score[e]	PHQ-9 Total Score[f]
Hemophilia affected relationship with (prospective) partners	0.287	0.28	0.307	0.274	**−0.398**	−0.251	−0.147	−0.323	−0.114[g]
Increasing satisfaction with support from partner regarding hemophilia	**−0.516**	**−0.494**	**−0.56**	**−0.528**	**0.537**	**0.426**	0.234	**0.473**	−0.127[g]
Hemophilia affected the quality of sex life	**0.508**	**0.479**	**0.468**	0.369	−0.302	−0.233[g]	−0.162[g]	−0.253	−0.119[g]
Increasing satisfaction with support from friends	**−0.387**	**−0.397**	**−0.419**	**−0.426**	**0.458**	0.326	0.222	**0.4**	0.002[g]
Negative experiences with telling friends about hemophilia	**0.388**	**0.44**	**0.428**	**0.41**	**−0.49**	**−0.449**	−0.29	**−0.478**	−0.009[g]
Bullied by peers because of hemophilia	**0.459**	**0.509**	**0.49**	**0.442**	**−0.527**	**−0.508**	−0.334	**−0.52**	−0.080[g]
Negative experiences with telling colleagues at work/school about hemophilia	0.351	**0.384**	0.368	0.367	**−0.436**	−0.333	−0.253	**−0.397**	−0.074[g]
Bullied by colleagues at work/school because of hemophilia	0.286	0.321	0.315	0.309	**−0.408**	−0.363	−0.215	**−0.391**	−0.208

Notes: [a]Range, −0.011–1.0 (higher scores indicate better quality of life or functional status). [b]Range, 0–10 (higher scores indicate greater pain severity or pain interference). [c]Pain severity score is the average of 4 severity scores (worst, least, average, current). [d]Pain interference score is the average of 7 interference scores. [e]Range, 0–100 (higher scores indicate better quality of life or functional status). [f]Range, 0–27 (higher scores indicate more severe depression). [g]Not significant. Negative attributes are shown in red. Inverse correlations are highlighted in gray. Correlations highlighted in bold are considered high ($r \geq 0.37$).

Abbreviations: BPI, Brief Pain Inventory v2 Short Form; HAL, Hemophilia Activities List; PHQ-9, Patient Health Questionnaire; VAS, visual analog scale.

Table 4 Pearson correlation assessment between the psychological/stress impact of hemophilia and PRO scores in adults with hemophilia B

Survey Question	EQ-5D-5L Mobility	EQ-5D-5L Self-care	EQ-5D-5L Usual Activities	EQ-5D-5L Pain/ Discomfort	EQ-5D-5L Anxiety/ Depression	EQ-5D-5L Index Score[a]	EQ-5D-5L Overall Health VAS Score	BPI Worst Pain[b]	BPI Least Pain[b]
Experienced stressful events: loss of job	**0.401**	**0.393**	**0.613**	**0.581**	**0.621**	**−0.582**	**−0.445**	**0.539**	**0.599**
Received psychological treatment in the past 5 years	**0.448**	**0.441**	**0.632**	**0.624**	**0.606**	**−0.597**	**−0.488**	**0.588**	**0.62**
Psychological treatment related to hemophilia	0.015[g]	0.228	0.151[g]	0.176	0.328	−0.211	−0.271	0.232	**0.394**

Survey Question	BPI Average Pain[b]	BPI Current Pain[b]	BPI Pain Severity[c]	BPI Pain Interference[d]	HAL Upper Extremity[e]	HAL Basic Lower Extremity[e]	HAL Complex Lower Extremity[e]	HAL Overall Score[e]	PHQ-9 Total Score[f]
Experienced stressful events: loss of job	**0.667**	**0.639**	**0.668**	**0.65**	−0.269	−0.275	−0.162	−0.304	**0.694**
Received psychological treatment in the past 5 years	**0.67**	**0.629**	**0.681**	**0.676**	−0.311	−0.308	−0.248	−0.364	**0.7**
Psychological treatment related to hemophilia	0.332	0.29	**0.371**	**0.39**	−0.239	−0.104[g]	0.001[g]	−0.135[g]	0.307

Notes: [a]Range, −0.011–1.0 (higher scores indicate better quality of life or functional status). [b]Range, 0–10 (higher scores indicate greater pain severity or pain interference). [c]Pain severity score is the average of 4 severity scores (worst, least, average, current). [d]Pain interference score is the average of 7 interference scores. [e]Range, 0–100 (higher scores indicate better quality of life or functional status). [f]Range, 0–27 (higher scores indicate more severe depression). [g]Not significant. Negative attributes are shown in red. Inverse correlations are highlighted in gray. Correlations highlighted in **bold** are considered high ($r \geq 0.37$).

Abbreviations: BPI, Brief Pain Inventory v2 Short Form; HAL, Hemophilia Activities List; PHQ-9, Patient Health Questionnaire; VAS, visual analog scale.

Table 5 Pearson correlation assessment between access to and responsibility for hemophilia treatment and PRO scores in adults with hemophilia B

Survey Question	EQ-5D-5L Mobility	EQ-5D-5L Self-care	EQ-5D-5L Usual Activities	EQ-5D-5L Pain/ Discomfort	EQ-5D-5L Anxiety/ Depression	EQ-5D-5L Index Score[a]	EQ-5D-5L Overall Health VAS Score	BPI Worst Pain[b]	BPI Least Pain[b]
Access to and responsibility for factor/treatment									
Self-responsibility for your hemophilia care (vs somebody else)	−0.326	**−0.474**	**−0.394**	−0.244	**−0.394**	**0.487**	**0.561**	−0.317	**−0.528**
Routine factor treatment (vs on-demand)	0.36	**0.453**	0.335	0.293	**0.414**	**−0.502**	**−0.468**	**0.411**	**0.459**
Difficulty obtaining or concerns about factor products' availability or affordability									
Last 5 years	0.289	**0.399**	**0.617**	**0.498**	**0.53**	**−0.483**	**−0.454**	**0.511**	**0.62**
Next 5 years	0.323	0.351	**0.399**	0.232	0.366	**−0.449**	**−0.57**	0.279	**0.459**
Lack of control[h]	−0.27	−0.309	−0.133	−0.038[g]	−0.172	0.279	0.368	−0.002[g]	−0.013[g]
Access to HTC									
Fewer visits to HTC in the past year	0.237	0.077[g]	0.26	**0.447**	0.327	−0.229	−0.061[g]	0.319	0.24

Survey Question	BPI Average Pain[b]	BPI Current Pain[b]	BPI Pain Severity[c]	BPI Pain Interference[d]	HAL Upper Extremity[e]	HAL Basic Lower Extremity[e]	HAL Complex Lower Extremity[e]	HAL Overall Score[e]	PHQ-9 Total Score[f]
Access to and responsibility for factor/treatment									
Self-responsibility for your hemophilia care (vs somebody else)	**−0.481**	**−0.494**	**−0.506**	**−0.44**	**0.503**	**0.381**	0.236	**0.466**	0.045[g]
Routine factor treatment (vs on-demand)	**0.486**	**0.471**	**0.498**	**0.43**	**−0.459**	**−0.452**	−0.292	**−0.456**	−0.011[g]
Difficulty obtaining or concerns about factor products' availability or affordability									
Last 5 years	**0.611**	**0.564**	**0.631**	**0.625**	−0.257	−0.157	−0.123	−0.246	**0.657**
Next 5 years	**0.41**	**0.414**	**0.432**	**0.422**	**−0.44**	−0.299	−0.186	**−0.38**	−0.006[g]
Lack of control[h]	0.028[g]	−0.022[g]	−0.004[g]	−0.081[g]	**0.445**	**0.45**	**0.403**	**0.449**	0.31
Access to HTC									
Fewer visits to HTC in the past year	0.272	0.283	0.295	0.293	0.079[g]	−0.024[g]	−0.025[g]	0.009[g]	**0.633**

Notes: [a]Range, −0.011–1.0 (higher scores indicate better quality of life or functional status). [b]Range, 0–10 (higher scores indicate greater pain severity or pain interference). [c]Pain severity score is the average of 4 severity scores (worst, least, average, current). [d]Pain interference score is the average of 7 interference scores. [e]Range, 0–100 (higher scores indicate better quality of life or functional status). [f]Range, 0–27 (higher scores indicate more severe depression). [g]Not significant. [h]Respondents rated disease control on a scale of 0–10, with 0 indicating "not at all" and 10 indicating "extremely well." Negative attributes are shown in red. Inverse correlations are highlighted in gray. Correlations highlighted in **bold** are considered high ($r \geq 0.37$).

Abbreviations: BPI, Brief Pain Inventory v2 Short Form; HAL, Hemophilia Activities List; HTC, hemophilia treatment center; PHQ-9, Patient Health Questionnaire; VAS, visual analog scale.

5D-5L Index/VAS, HAL Overall); future access problems were weakly associated with depression (PHQ-9; Table 5).

Interestingly, fewer visits to the hemophilia treatment center (HTC) in the past year was strongly correlated with worsening pain as measured by the EQ-5D-5L and worsening depressive symptoms, as measured by the PHQ-9 (Table 5).

The number of bleeds or joint bleeds in the past year did not appear to be strongly correlated with overall HRQoL, pain, anxiety, depression, or change in functional capabilities. Similarly, reporting a specific joint that bleeds more (eg, target joint) was not strongly correlated with HRQoL (Table S3).

Caregivers of children with hemophilia B

B-HERO-S included 150 caregivers (34 men, 116 women) of affected children with hemophilia B (121 boys, 29 girls). Demographics and treatment characteristics have been previously reported[12] with the majority of children having moderate (56%) or mild (18%) hemophilia. PRO results including PHQ-9 and GAD-7 have been previously reported.[27]

Correlations between PROs and psychosocial and functional questions

Caregiver/spouse/partner work

Caregivers (or their spouse/partner) were asked to evaluate multiple aspects of hemophilia's impact on their work. All work-related negative impacts of the disease were associated with increased symptoms of depression (PHQ-9) and/or anxiety (GAD-7) in caregivers. Strong correlations were seen between being overlooked for promotion, not hired for a job, unable to work because of the child's specific treatment, and not being able to work flexible hours and depression/anxiety measures. Having to leave a job due to hemophilia was strongly associated with anxiety symptoms (GAD-7) but not depressive symptoms; not being able to restrict number of work hours was also weakly correlated with anxiety (Table 6).

Child's functional and recreational activities

Two questions originally from the CDC UDC questionnaire[11] (increasing limitation in the child's functional abilities and engagement in activities, increasing number of days of missed school/work because of upper extremity problems in the prior 6 months) were both strongly correlated with symptoms of depression (PHQ-9) and anxiety (GAD-7) in caregivers. However, there was only a moderate correlation between increasing treatment adjustment to allow for recreational activities and anxiety in caregivers, and only a weak correlation of increasing negative experiences upon the child's engagement in recreational activities with anxiety and depression in caregivers (Table 6).

Family and other relationships

Both the caregiver's report of negative experiences telling somebody that their child has hemophilia and the child's experience of negative reactions telling somebody he/she has hemophilia were strongly correlated with caregiver depression and anxiety. Furthermore, caregivers reporting their child was bullied because of having hemophilia were strongly correlated with caregiver anxiety and depression. However, no relationship was found between hemophilia's negative impact on the caregivers' other children and caregiver anxiety or depression (Table 6).

Psychological/stress

One of the strongest correlations was observed between caregiver report of the child having received psychological treatment in the past 5 years and caregiver depression and anxiety (both >0.7); the treatment being directly related to hemophilia was also strongly correlated. Strong, positive correlations were seen between experiencing stressful events, particularly the loss of a job due to caring for a child with hemophilia (>0.75), and caregiver depression/anxiety; however, financial problems were not strongly correlated with depression/anxiety (Table 6).

Access to factor/treatment and HTC

Strong, positive correlations were seen between caregiver concerns regarding access to factor in the past 5 years due to availability or affordability and depression/anxiety; concerns about access in the next 5 years were weakly correlated with caregiver depression and anxiety. A strong, positive correlation was seen between having fewer visits to the HTC in the past year and caregiver depression; increasing difficulty with their child visiting the HTC was weakly correlated with caregiver depression (Table 6).

Discussion

Studying the psychosocial impact of hemophilia in population-level studies has in the past required researchers to rely on descriptive analyses of answers to a small number of questions that aim to characterize patient and caregiver/family stories. Such approaches have supported efforts of advocacy organizations and provided the framework for

Table 6 Pearson correlation assessment between impact of hemophilia and PRO scores in caregivers of children with hemophilia B

Survey Question	PHQ-9[a] (Depression)	GAD-7[b] (Anxiety)
Impact on work due to caring for a child with hemophilia		
CG or SP had to leave job	0.338	**0.393**
CG or SP overlooked for promotion	**0.611**	**0.649**
CG or SP not hired for a job	**0.648**	**0.67**
CG or SP not able to work because of child's specific treatment regimen	**0.495**	**0.529**
CG or SP not able to restrict number of hours	0.34	0.291
CG or SP not able to work flexible hours	**0.416**	**0.37**
Impact on functional and recreational activities		
Increasing limitation in child's functional abilities and engagement in activities	**0.394**	**0.441**
Increasing number of days child missed school/work because of upper extremity problems in prior 6 months[c]	**0.431**	**0.476**
Increasing negative impact on your child engaging in recreational activities	0.131[d]	0.182
Increasing treatment adjustment to allow for recreational activities	0.326	0.369
Impact on family and relationships		
Negative impact of hemophilia on your other children	0.173[d]	0.221[d]
CG negative experiences telling someone that your child has hemophilia	**0.399**	**0.465**
Child had a negative reaction telling someone he/she has hemophilia	**0.557**	**0.611**
Child bullied as a result of having hemophilia	**0.522**	**0.59**
Psychological/stress		
Received psychological treatment in the past 5 years	**0.706**	**0.721**
Psychological treatment related to hemophilia	**0.418**	**0.459**
Experienced stressful events		
Loss of job	**0.755**	**0.783**
Financial problems	0.36	0.288
Any other stressful event	**0.658**	**0.627**
Access to factor/treatment		
Difficulty obtaining or concerns about factor products' availability or affordability		
Last 5 years	**0.468**	**0.559**
Next 5 years	0.259	0.297
Access to HTC		
Fewer visits to HTC in the past year	**0.398**	0.343
Increasing difficulty for child to visit the HTC	0.303	0.305

Notes: [a]Range, 0–27 (higher scores indicate more severe depression). [b]Range, 0–21 (higher scores indicate more severe anxiety). [c]Impact of lower extremity problems was considered independently of upper extremity problems. [d]Not significant. Correlations highlighted in bold are considered high ($r \geq 0.37$).
Abbreviations: CG, caregiver; GAD-7, Generalized Anxiety Disorder 7-item [scale]; HTC, hemophilia treatment center; PHQ-9, Patient Health Questionnaire; SP, spouse/partner.

patient, caregiver, and provider education around unmet needs. However, discrepancies between more historical questions (eg, ever having had negative experiences with relationships, schools, employers, or friends/peers) and more present-time questions (eg, satisfaction with current relationships, job, employer, friends/peers) led us to add qualifying questions to better understand these relationships in B-HERO-S (eg, Did prior negative experiences impact your current relationships/employment? Choice of partner/spouse/friends/career?).

Assessing PROs using well-established measures in adult patients and caregivers of affected children[10,12,28,29] adds another level of information that we expected to correlate with the traditional measures of hemophilia's impact.

The B-HERO-S study demonstrated strong correlations between pain, depression, and anxiety and many questions that are routinely asked of patients and caregivers of children in the comprehensive care setting, despite the fact that the recall periods for PRO instruments were short term ("today" up to 1 month) and for psychosocial questions were long term ("ever," past 5 years). This observation highlights the potential long-lasting effects of these events and experiences on individuals' current health status.

In adult patients, lower overall health today as measured by the EQ-5D-5L Index/VAS was associated with many short- and long-term impact questions. The associations between pain and the psychosocial impact of hemophilia were especially notable, as pain severity and interference are typically thought to be more impactful in individuals with severe hemophilia. The B-HERO-S study showed that pain remains an important aspect of HRQoL that should be measured and accounted for, even in studies of individuals with mild or moderate hemophilia B. In both adult patients and caregivers, responses significantly associated with depression/anxiety seemed to reflect acutely impactful issues (eg, recent problems related to functional impairment or disability, recent difficulty or concerns with factor availability) versus more historical issues (eg, negative experiences in telling others about their or their child's hemophilia, being bullied or their child being bullied because of hemophilia).

Analysis of simple correlations is limited in that it does not address causality or account for covariates such as disease severity and treatment regimen. This was possible in the modeling analysis from the P-FiQ study, in which the authors were able to control for joint status assessed by HJHS. In addition, the present analysis of B-HERO-S cannot account for the presence or severity of joint disease, but presumably, the population of adults with mild-moderate hemophilia would be expected to have less severe joint disease than those with severe hemophilia.[30] The possibility that adults with mild-moderate hemophilia can develop arthropathy that has psychosocial impact and reduces HRQoL is supported by recent epidemiological studies showing bleeding in individuals with up to 15–30% baseline factor activity levels.[31,32] Current HRQoL measures of pain and functional impairment strongly correlated with impact of hemophilia on employment, having lost a job, or having negative experiences with employers or colleagues, suggesting that the respondents may represent those with a moderate phenotype and arthropathy. However, feeling supported by employers and colleagues at work was associated with lower pain scores, suggesting, as in P-FiQ, a possible benefit to working.

One finding that seems consistent across cross-sectional surveys is that more extensive treatment for hemophilia is associated with worse HRQoL, presumably because increased treatment serves as a surrogate marker of a more severe phenotype with a more pronounced negative impact on the domains that comprise HRQoL.[3,7,27,33,34] In this analysis, we identified in adults associations between measures of pain and functional impairment and self-responsibility for hemophilia care and self-infusion, taking some form of routine treatment to prevent bleeding, having had issues with access to factor in the past 5 years, and anticipating issues with access in the next 5 years. For caregivers, we identified associations between having prior issues with access to factor and depression and anxiety.

This analysis provides insights into the importance of the qualitative psychosocial review conducted by members of the comprehensive care team compared with routine assessment of HRQoL using PRO instruments in the clinical setting. An open-ended interview offers the opportunity to identify current issues that the patient or family might be facing and to determine whether any of these issues can be addressed by the center, such as providing education to others (eg, schools, employers) to mitigate negative experiences or bullying. PRO measures, by contrast, provide an important means to quantify the impact of an intervention over time, such as a pain management plan, course of physiotherapy, or psychological counseling. In this way, measures of HRQoL domains can provide a framework for ongoing assessment of progress toward treatment goals. PRO instruments that are designed to be used as screening tools (such as the PHQ-9 and GAD-7) may also provide a means of identifying important topics that should be addressed by the comprehensive care team. The use of screening tools has proven effective in care settings outside the HTC and should be considered in the hemophilia population.

There are several limitations to the B-HERO-S data that have been previously described, including recruitment bias. Participants for this study were recruited through hemophilia advocacy organizations via social media and email, which may have led to enrollment of patients with mild-moderate hemophilia with a more severe phenotype who were more likely to seek support from and be involved in the hemophilia B community.[12,27,33] In addition, as noted in this discussion, the associations identified

in this study do not prove causation; however, they do suggest avenues for further investigation and a need for further refining questions on hemophilia psychosocial impact to identify current issues that must be addressed to improve HRQoL.

Conclusion

This post hoc analysis of data from the B-HERO-S study revealed strong associations between questions related to the psychosocial impact of hemophilia and HRQoL domains, as assessed by PRO instruments in a largely mild-moderate hemophilia population. Although these associations do not imply causality, they reinforce the necessity of ongoing psychosocial assessments, including HRQoL issues, during comprehensive care visits. Individualized psychosocial interventions and/or referrals should be implemented accordingly to optimize psychosocial well being, including HRQoL. Ongoing use of validated PRO instruments, especially those specifically developed for people with hemophilia, aids in the identification of current issues affecting HRQoL and the ability to measure effectiveness of treatment.

Abbreviations

AD, anxiety/depression; AP, average pain; BLE, basic lower extremity; B-HERO-S, Bridging Hemophilia B Experiences, Results and Opportunities into Solutions; BPI, Brief Pain Inventory v2 Short Form; CDC, Centers for Disease Control and Prevention; CLE, complex lower extremity; CP, current pain; GAD-7, Generalized Anxiety Disorder 7-Item; HAL, Hemophilia Activities List; HERO, Hemophilia Experiences, Results and Opportunities; HJHS, Hemophilia Joint Health Score; HRQoL, health-related quality of life; HTC, hemophilia treatment center; LP, least pain; MO, mobility; PD, pain/discomfort; P-FiQ, Pain, Functional Impairment, and Quality of Life; PHQ-9, Patient Health Questionnaire; PI, pain interference composite score; PRO, patient-reported outcome; PS, pain severity composite score; SC, self-care; SF-36, 36-Item Short Form Survey; UA, usual activities; UE, upper extremity; UDC, Universal Data Collection; VAS, visual analog scale; WP, worst pain.

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Disclosure

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References

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1–e47. doi:10.1111/j.1365-2516.2012.02909.x
2. Luck JV Jr., Silva M, Rodriguez-Merchan EC, Ghalambor N, Zahiri CA, Finn RS. Hemophilic arthropathy. *J Am Acad Orthop Surg*. 2004;12(4):234–245.
3. Forsyth AL, Witkop M, Lambing A, et al. Associations of quality of life, pain, and self-reported arthritis with age, employment, bleed rate, and utilization of hemophilia treatment center and health care provider services: results in adults with hemophilia in the HERO study. *Patient Prefer Adherence*. 2015;9:1549–1560. doi:10.2147/PPA.S87659
4. Neufeld EJ, Recht M, Sabio H, et al. Effect of acute bleeding on daily quality of life assessments in patients with congenital hemophilia with inhibitors and their families: observations from the dosing observational study in hemophilia. *Value Health*. 2012;15(6):916–925. doi:10.1016/j.jval.2012.05.005
5. Witkop M, Neff A, Buckner TW, et al. Self-reported prevalence, description and management of pain in adults with haemophilia: methods, demographics and results from the Pain, Functional Impairment, and Quality of Life (P-FiQ) study. *Haemophilia*. 2017;23(4):556–565. doi:10.1111/hae.13214
6. Kempton CL, Buckner TW, Fridman M, Iyer NN, Cooper DL. Factors associated with pain severity, pain interference, and perception of functional abilities independent of joint status in US adults with hemophilia: multivariable analysis of the Pain, Functional Impairment, and Quality of Life (P-FiQ) study. *Eur J Haematol*. 2018;100(Suppl 1):25–33. doi:10.1111/ejh.13025

7. Buckner TW, Batt K, Quon D, et al. Assessments of pain, functional impairment, anxiety, and depression in US adults with hemophilia across patient-reported outcome instruments in the Pain, Functional Impairment, and Quality of Life (P-FiQ) study. *Eur J Haematol*. 2018;100(Suppl 1):5–13. doi:10.1111/ejh.13027
8. Forsyth AL, Gregory M, Nugent D, et al. Haemophilia Experiences, Results and Opportunities (HERO) study: survey methodology and population demographics. *Haemophilia*. 2014;20(1):44–51. doi:10.1111/hae.12239
9. Plug I, Mauser-Bunschoten EP, Brocker-Vriends AH, et al. Bleeding in carriers of hemophilia. *Blood*. 2006;108(1):52–56. doi:10.1182/blood-2005-09-3879
10. Kempton CL, Wang M, Recht M, et al. Reliability of patient-reported outcome instruments in US adults with hemophilia: the Pain, Functional Impairment and Quality of Life (P-FiQ) study. *Patient Prefer Adherence*. 2017;11:1603–1612. doi:10.2147/PPA.S141389
11. Centers for Disease Control and Prevention. Report on the Universal Data Collection Program, 2005–2009. 2014:1–26. Available from: www2a.cdc.gov/ncbddd/htcweb/UDC_Report/UDC_Report.asp. Accessed January 18, 2019.
12. Buckner TW, Witkop M, Guelcher C, et al. Management of US men, women, and children with hemophilia and methods and demographics of the Bridging Hemophilia B Experiences, Results and Opportunities into Solutions (B-HERO-S) study. *Eur J Haematol*. 2017;98(Suppl 86):5–17. doi:10.1111/ejh.12854
13. Cassis FR, Querol F, Forsyth A, Iorio A, HERO International Advisory Board. Psychosocial aspects of haemophilia: a systematic review of methodologies and findings. *Haemophilia*. 2012;18(3):e101–e114. doi:10.1111/j.1365-2516.2011.02683.x
14. Palareti L, Poti S, Cassis F, Emiliani F, Matino D, Iorio A. Shared topics on the experience of people with haemophilia living in the UK and the USA and the influence of individual and contextual variables: results from the HERO qualitative study. *Int J Qual Stud Health Well-being*. 2015;10:28915. doi:10.3402/qhw.v10.28915
15. Poti S, Palareti L, Cassis FR, Brondi S. Health care professionals dealing with hemophilia: insights from the international qualitative study of the HERO initiative. *J Multidiscip Healthc*. 2019;12:361–375. doi:10.2147/JMDH.S201759
16. Cassis FR, Buzzi A, Forsyth A, et al. Haemophilia Experiences, Results and Opportunities (HERO) study: influence of haemophilia on interpersonal relationships as reported by adults with haemophilia and parents of children with haemophilia. *Haemophilia*. 2014;20(4):e285–e295. doi:10.1111/hae.12454
17. Buzzi A, Kelley L, Gregory M, Skinner M, Kalnins W. Improving comprehensive care in the haemophilia community: building on the HERO study. *Haemophilia*. 2016;22(4):e320–e322. doi:10.1111/hae.12945
18. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727–1736. doi:10.1007/s11136-011-9903-x
19. Devlin NJ, Krabbe PF. The development of new research methods for the valuation of EQ-5D-5L. *Eur J Health Econ*. 2013;14(Suppl 1):S1–S3. doi:10.1007/s10198-013-0502-3
20. EuroQoL EQ-5D-5L index value calculator. Available from: http://euroqol.org. Accessed December 12, 2018.
21. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–613. doi:10.1046/j.1525-1497.2001.016009606.x
22. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092–1097. doi:10.1001/archinte.166.10.1092
23. Cleeland C The Brief Pain Inventory user guide. Houston, Texas: MD Anderson Cancer Center; 2009. Available from: https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools/brief-pain-inventory.html. Accessed December 12, 2018.
24. van Genderen FR, Westers P, Heijnen L, et al. Measuring patients' perceptions on their functional abilities: validation of the Haemophilia Activities List. *Haemophilia*. 2006;12(1):36–46. doi:10.1111/j.1365-2516.2006.01186.x
25. Guidelines for data processing and analysis of the International physical activity questionnaire (IPAQ) - short and long forms; 2005. Available from: https://sites.google.com/site/theipaq/scoring-protocol. Accessed December 12, 2018.
26. Cohen J. A power primer. *Psychol Bull*. 1992;112(1):155–159.
27. Buckner TW, Witkop M, Guelcher C, et al. Impact of hemophilia B on quality of life in affected men, women, and caregivers-Assessment of patient-reported outcomes in the B-HERO-S study. *Eur J Haematol*. 2018;100(6):592–602. doi:10.1111/ejh.13055
28. Buckner TW, Wang M, Cooper DL, Iyer NN, Kempton CL. Known-group validity of patient-reported outcome instruments and hemophilia joint health score v2.1 in US adults with hemophilia: results from the Pain, Functional Impairment, and Quality of Life (P-FiQ) study. *Patient Prefer Adherence*. 2017;11:1745–1753. doi:10.2147/PPA.S141392
29. Batt K, Recht M, Cooper DL, Iyer NN, Kempton CL. Construct validity of patient-reported outcome instruments in US adults with hemophilia: results from the Pain, Functional Impairment and Quality of Life (P-FiQ) study. *Patient Prefer Adherence*. 2017;11:1369–1380. doi:10.2147/PPA.S141390
30. Knobe K, Berntorp E. Haemophilia and joint disease: pathophysiology, evaluation, and management. *J Comorb*. 2011;1:51–59.
31. Soucie JM, Monahan PE, Kulkarni R, Konkle BA, Mazepa MA, US Hemophilia Treatment Center Network. The frequency of joint hemorrhages and procedures in nonsevere hemophilia A vs B. *Blood Adv*. 2018;2(16):2136–2144. doi:10.1182/bloodadvances.2018020552
32. den Uijl IE, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: the association of joint bleeds according to baseline FVIII activity levels. *Haemophilia*. 2011;17(1):41–44. doi:10.1111/j.1365-2516.2010.02383.x
33. Buckner T, Witkop M, Guelcher C, et al. Impact of mild to severe hemophilia B on quality of life including pain and functional abilities in affected men/women and caregivers of affected boys/girls: analysis of patient reported outcomes in the Bridging Hemophilia B Experiences, Results, and Opportunities into Solutions (B-HERO-S) study. *Blood*. 2016;128:251. doi:10.1182/blood-2016-06-724161
34. Kempton C, Recht M, Neff A, et al. Impact of pain and functional impairment in US adult people with hemophilia (PWH): patient-reported outcomes and musculoskeletal evaluation in the Pain, Functional Impairment, and Quality of Life (P-FiQ) study. *Blood*. 2015;126(23):39.